REMARKS

Claims 25-28 and 35-40 are pending in this application.

Applicants respectfully request that the Examiner consider the following remarks in response to the final Office action mailed November 2, 2004 and the Examiner's Answer to Appellant's Brief mailed January 5, 2006.

Rejection under 35 U.S.C. § 101:

The final Office action mailed November 2, 2004 rejected claims 25-28 and 35-40 under 35 U.S.C. § 101 for lack of utility because (1) allegedly the MLR assay is an *in vitro* assay and as such did not support a claim that a compound that tested positive in the MLR assay would have an *in vivo* effect; and (2) allegedly the specification fails to disclose sufficient detail about the MLR assay, including what controls were used and what data was collected. The Examiner's Answer mailed January 5, 2006 concedes, in view of US Patent No. 5,817,306, "that the MLR assay is art recognized for identifying molecules which suppress an immune response." (Page 6, Examiner's Answer). Applicants thank the Examiner for this acknowledgement and note that other patent literature, including US Patent No. 5,648,376 at col. 11, ll 24-27; US Patent No. 5,801,193 at col. 8, ll. 6-15; US Patent No. 6,472,518 at col. 20, ll 21-25, and US Patent No. 6,743,014 at col. 21, ll 16-18 recognize the MLR assay as an *in vitro* predictor of *in vivo* immunosuppressant activity.

Although the Examiner's Answer recognizes the MLR assay as a valid predictor of an *in vivo* immunosuppressant utility, the Examiner's Answer maintains that claims 25-28 and 35-40 still are not supported by an adequate utility because allegedly the specification does not provide sufficient details about the MLR assay, including what controls were used, how the CD4-Ig control was used, and what the resulting data and values were indicating that the PRO361 polypeptide tested "positive" in the MLR assay.

Applicants respectfully disagree with the Examiner's assertion that claims 25-28 and 35-40 are not supported by an adequate utility. Significantly, Applicants have asserted a utility of PRO361 based on results of an MLR assay and "[i]n most cases, an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the

utility requirement of 35. U.S.C. 101." MPEP § 2107.02(III)(A) (citations omitted). Indeed, according to the Court of Customs and Patent Appeals the standard for accepting the credibility of an applicant's assertion of utility is that "a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer,* 503, F.2d 1380, 1391 (CCPA 1965) (emphasis original). Thus, Office personnel are directed to presume that a statement of utility by an applicant is true and to overcome the presumption of truth that an assertion of utility by an Applicant enjoys, Office personnel must establish that it is more likely than not that one of ordinary skill in the art would doubt (*i.e.,* "question") the truth of the statement of utility. According to § 2107.02 of the MPEP, "[t]o do this, Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered 'false' by a person of ordinary skill in the art."

The only basis provided for the assertion that one of skill in the art would question the truth of Applicants' assertion of utility, or consider it false, is that the specification does not provide sufficient detail about the MLR assay, specifically controls used and data obtained, for one of ordinary skill in the art to independently evaluate Applicants' conclusion that the PRO361 polypeptide has immunosuppressive characteristics. However, when the evidence is viewed in total, as it must be, this is not a sufficient basis for finding that claims 25-28 and 35-40 lack utility. Although the specification may not provide actual data values for levels of immunosuppression achieved using the PRO361 polypeptide in the MLR assay, the specification does provide ample description of the MLR assay, including description of the controls used in the assay, and ample description of how to evaluate results obtained from the MLR assay data. Indeed, in view of the significant teachings in the specification and the articles incorporated therein by reference, as well as the high level of skill and understanding in the art as demonstrated by art references discussed below, the lack of explicit data does not make it more likely than not that one of ordinary skill in the art would doubt Applicants' assertion of utility.

For example, at page 141 of the specification Applicants disclose that the basic MLR assay protocol followed in conducting the experiment described in Example 34 of the specification is described in *Current Protocols in Immunology,* unit 3.12; edited by J. E. Coligan *et al.,* National Institutes of Health, Published by John Wiley & Sons, Inc, the entirety of which is incorporated into the present specification by reference. Because *Current Protocols in Immunology* is incorporated by reference into the specification, its teachings must be viewed as part of the disclosure of the specification. In addition to the description of the MLR assay protocol found in the *Current Protocols* reference, the specification describes procedures for isolating PBMCs from human and murine donors, as well as plating conditions. Thus, the description of the MLR assay found at page 141 of the specification provides sufficient detail about how the assay was carried out in determining that PRO361 is an immunosuppressant. As further evidence that the description in the specification, which incorporates the disclosure in *Current Protocols in Immunology,* is sufficient, Applicants respectfully direct the Examiner's attention to U.S. Patent No. 5,958,403, col. 6, ll 20-21, which explains that the MLR assay is performed as described in *Current Protocols in Immunology.*

Further, the specification discloses sufficient information about the controls used with the MLR assay. For example, page 3.12.7 of *Current Protocols in Immunology,* which is incorporated into the specification by reference, states:

> Separate wells with control cultures should be set up that include – for each dose of responder and stimulator cells – replicate wells of responder cells with irradiated or mitomycin C-treated syngeneic stimulator cells. Values obtained from these controls reflect "background" proliferation values (see step 9 of the basic protocol). Other negative controls often included are wells with stimulator cells alone and wells with responder cells alone. These are not used for the calculation of the data, but are useful to compare with background proliferation values; the latter should not be much higher (<2-fold) than those obtained with stimulator or responder cells alone. Higher background values indicate potential autoreactivity.

At page 141 of the specification, Applicants disclose that the procedure followed in carrying out the MLR assay of Example 34 is forth in *Current Protocols in Immunology.* Therefore, one of ordinary skill in the art would understand that the controls discussed

above were used in carrying out the MLR assay with the PRO361 polypeptide. Further, the specification discloses that additional controls including either 100 microliters of cell culture media or 100 microliters of CD4-IgG were used. The Examiner's Answer alleges that it is not clear how CD4-IgG would control for background stimulation or provide for a measure of maximal stimulation. However, Applicants respectfully maintain that one of ordinary skill in the art would appreciate that CD4-IgG is an antibody that might be used as a negative control by blocking or preventing activation of allogeneic responder cells. Additionally, skilled artisans would appreciate that cell culture media would serve as a control by providing a measure of background levels. As quoted above from *Current Protocols,* other useful controls are those that can be used for comparison with background proliferation values (*e.g.,* culture media and CD4-IgG). Controls such as those used in the MLR assay described in the specification help ensure that statistically significant results are obtained.

Significantly, the controls disclosed in *Current Protocols* and used by Applicants are art recognized as sufficient controls for use in the MLR assay. For example, in the MLR assay described in U.S. Patent No. 5,648,376, several controls similar to those described in the *Current Protocols in Immunology* reference were used, including addition of irradiated responder cells to responder cells with or without the test compound and evaluation of wells containing either only irradiated responder or only stimulator cells. *See e.g.,* col. 17, ll. 52-57 of US Patent No. 5,648,376. Further, Applicants respectfully submit that the discussion of controls presented in the present specification is sufficient given the level of skill and knowledge in the art of the MLR assay because there are several patent references discussing the MLR assay, and relying on the results of that assay for utility support, that do not provide any detail regarding what, if any controls were used, or how such controls were used. *See e.g.,* US Patent No. 5,801,193, cols. 8-9; US Patent No. 6,734,014, col. 34, ll. 45-56; and US Patent No. 4,950,647, cols. 6-8.

In addition to explaining how to conduct the MLR assay, Example 34 of the present specification, through reference to the *Current Protocols in Immunology,* also explains how to calculate the results obtained from the MLR assay. Specifically, the data is

computed as the difference in cpm of stimulated (experimental) and control (no test substance added) cultures. This is done by subtracting the arithmetic mean of cpm from triplicate control cultures from the arithmetic mean of cpm from corresponding test cultures. Alternatively, the data may be calculated as the ratio of cpm of test and control cultures. This is done by dividing the arithmetic mean of cpm from stimulated cultures by the arithmetic mean of cpm from control cultures. Thus, Applicants have provided sufficient detail in the specification, either explicitly or through incorporation by reference, about the MLR assay, how the assay is performed, what controls are used and how they are used, and how the data is calculated.

According to the specification, "[a]ny decreases below control is considered to be a positive result for an inhibitory compound, with decreases of less than or equal to 80% being preferred." This standard is art recognized for identifying compounds with immunosuppressive characteristics. For example, in his declaration, Dr. Sherman Fong, Ph.D. explains that it is his scientific opinion that "a PRO polypeptide shown to inhibit T-cell proliferation in the MLR assay where the activity is observed as 80% or less of the control, as specified in the present application, would be expected to find practical utility when an inhibition of the immune response is desired, such as in autoimmune diseases." (Page 3, paragraph 10 of the Fong Declaration (previously submitted)). In another example demonstrating that the specification sets forth an art recognized standard for identifying compounds with immune inhibitory activity, at col. 6, ll 16-19, U.S. Patent No. 5,958,403 states that "[u]seful constructs are also those which provide a mixed lymphocyte reaction (MLR) by decreasing proliferation by 20%, more preferably 40%, and most preferably by 60% relative to control cells."

The specification clearly states that PRO361 tested positive in the MLR assay. Therefore, although no explicit data is provided, in light of the significant details provided about the MLR assay, how it was performed, what controls were used, how they were used, and how the positive result was determined, one of ordinary skill in the art can conclude that PRO361 exhibited a level of inhibition greater than any inhibition seen with the controls and can conclude that PRO361 has immunosuppressant characteristics. This is sufficient to satisfy the utility requirement. As stated in *Nelson v.*

Bowler, 626 F.2d 853, 206 USPQ (BNA) 881 (C.C.P.A. 1980), tests evidencing pharmacological activity of a compound establish practical utility, even though they may not establish a specific therapeutic use.

Thus, although the specification may not provide actual data values for levels of immunosuppression achieved using the PRO361 polypeptide in the MLR assay, the specification does provide ample description of the MLR assay, including description of the controls used in the assay, and ample description of how to evaluate results obtained from the MLR assay data. Indeed, in view of these significant teachings and the high level of skill and understanding in the art, the lack of explicit data does not make it more likely than not that one of ordinary skill in the art would doubt Applicants' assertion of utility for the PRO361 polypeptide. Therefore, Applicants respectfully submit that claims 25-28 and 35-40 are supported by a specific, substantial and credible utility and respectfully request that this ground of rejection be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph:

Enablement

The final Office action and Examiner's Answer contend that because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention.

Applicants respectfully disagree. As discussed above, the claimed polypeptide has the specific, substantial, and credible utility of encoding a polypeptide which inhibits the proliferation of stimulated T-lymphocytes as demonstrated in the MLR assay experiment discussed in Example 34 at page 141 of the application. Applicants respectfully request the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112 ¶1 for alleged inadequate disclosure on how to use the claimed invention.

In the final Office action mailed November 2, 2004, Claim 40 is further rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement because "the specification does not disclose a repeatable process to obtain

the biological material and it is not apparent if the biological material is readily available to the public." The Examiner notes, however, that "Applicant has deposited the biological material, but there is no indication in the specification as to public availability." The Examiner kindly notes that "[if] the deposit is made under the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific biological materials will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement mad (sic) here." (Pages 6-7 of the Office action mailed November 2, 2004). Applicants submit herewith a declaration by Applicants, signed by Bonny G. Yeung, Ph.D., of Genentech, Inc. Applicants respectfully submit that this declaration overcomes this ground of rejection and respectfully request that it be withdrawn.

CONCLUSION

Applicants believe this Request for Continued Examination fully responds to the final Office action mailed November 2, 2004 and to the Examiner's Answer mailed January 5, 2006. Applicants respectfully request the Examiner grant allowance of pending claims 25-28 and 35-40. The Examiner is invited to contact the undersigned attorney for the Applicant via telephone if such communication would expedite allowance of this application.

Respectfully submitted,

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